

REMARKS

Status of Claims

Claims 1-4, 11-24 and 29-30 are pending in the application prior to the instant Amendment. Claims 19 and 20 are currently amended; claims 1-4 and 11-18 are canceled; claims 5-10 and 25-28 were previously canceled; and claim 24 is withdrawn from consideration; leaving claims 19-23 and 29-30 pending upon entry of the instant Amendment.

Specifically, as amended herein, claim 19 is merely a re-written independent form of the original claim 19 and includes all limitations of original claims 1, 3, 18 and 19. This amendment is made due to cancellations of original claims 1, 3 and 18 to expedite the prosecution of this application and not for patentability reasons. Support for these amendments can be found at least at claims 1, 3, 18 and 19 as originally filed. No new subject matter has been added.

As amended herein, claim 20 is merely a re-written independent form of the original claim 20 and includes all limitations of original claims 1, 3 and 20. This amendment is made due to cancellations of original claims 1 and 3 to expedite the prosecution of this application and not for patentability reasons. Support for these amendments can be found at least at claims 1, 3 and 20 as originally filed. No new subject matter has been added.

Applicants believe that all pending claims are in condition for allowance, as discussed in more detail below.

Telephonic Interview Summary

A telephonic interview between Examiner Sabiha N. Qazi and Applicants' attorney Yong Zhao was held on January 7, 2010. The patentability of pending claims was discussed and the Applicants' attorney presented arguments and explained the differences between compounds of instant claims, especially original claims 1, 20 and 29, and those of the prior art compounds cited by the Examiner in the Office Action. Applicants also proposed that original claims 1 and 3 can be canceled and leaving original claim 18 (by combining all limitations of original claims 1, 3 and 18) for further consideration to expedite the prosecution of this case. The Examiner invited the Applicants to submit amended claims for re-consideration.

Please note that as amended herein, original claim 19 (as presented in a re-written independent form by combining all limitations of original claims 1, 3, 18 and 19), which is narrower than original claim 18, is presented for further consideration to expedite the prosecution.

Information Disclosure Statement (IDS)

IDS forms were submitted by Applicants previously on 3/11/2005 and 11/19/2009. Applicants respectfully request the Examiner to consider all references on the submitted IDS forms and initial these references.

Co-pending Applications

A list of co-pending applications was submitted by the Applicants in the Response filed 7/23/2009.

Specification

No amendment is made to the specification.

Rejections under 35 U.S.C. §103(a)

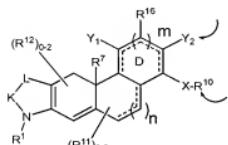
The Examiner rejected claims 1-4, 11-23, 29 and 30 under 35 U.S.C. §103(a) as being obvious over Kumar et al. (J. Med. Chem., 1993, 36, 3278-3285; hereinafter, "Kumar"), Schane et al. (Steroids, 1985, 45(2), 171-85; hereinafter, "Schane") and Bell et al. (US 4,349,558; hereinafter, "Bell"). (Office Action mailed November 16, 2009, page 3) Applicants respectfully traverse this rejection as none of the cited references, either alone or in combination, renders the pending claims obvious.

Claim 19

As an initial matter, Applicants respectfully point out that claim 19 is merely a re-written independent form of the original claim 19 and includes all limitations of original claims 1, 3, 18 and 19. This amendment is made due to cancellations of original claims 1, 3 and 18 to expedite the prosecution of this application. Additionally, the Examiner requested that Applicants disclose the prior art that is related to the provisos in the definitions of Y₂ and Y₃ in the original claim 1 (Office Action dated Nov. 16 2009, first paragraph on page 5). This request is moot in light of the instant amendments.

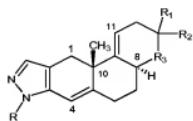
Claim 19 is not obvious over Kumar, Schane and Bell as compounds of claim 19 have substantially different structures from those disclosed by the cited art and none of the references would have provided any reason that would have led a skilled artisan to modify a known compound in the particular manner to arrive at the compounds of claim 19.

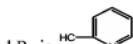
Claim 19 has the following general structure wherein Y₂ is CF₃ and R¹⁰ is selected from (1) phenyl, (2) benzyl, and (3) a 5-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N (wherein each of (1), (2) and (3) is optionally substituted with 1-3 substituents specified in the claim):



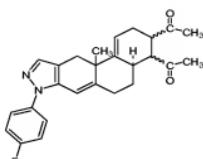
(Claim 19; arrows are added herein for better illustration).

The closest compounds disclosed by Kumar appear to be compounds 8-10 in Table 1 having the following general structure:



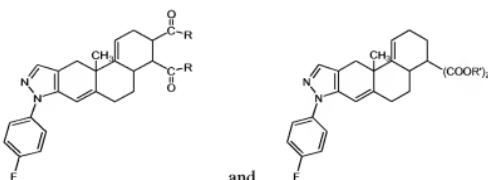
wherein R₁ and R₂ are H or Ac; and R₃ is  (Compound 8), CHAc (Compound 9) or C(CO₂Et)₂ (Compound 10). (Kumar, Table 1, page 3281)

The closest compound disclosed by Schane has the following structure:



(Schane, Figure 2, WIN 45164, page 173; hereinafter, "Compound 45164")

And the closest compounds disclosed by Bell have the following structures:



wherein R and R' are lower alkyl. (Bell, Abstract)

It can be seen that compounds of claim 19 can be distinguished from those disclosed in Kumar, Schane and Bell on at least two grounds:

First, Y₂ of claim 19 is CF₃. On the other hand, the structurally closest compounds in Kumar, Schane and Bell have H (compounds 8 and 10 of Kumar), Ac (compound 9 of Kumar); -C(O)CH₃ (compound 45,164 of Schane); and -C(O)R or H (Bell) at the same position (Kumar, Table 1, page 3281; Schane, Figure 2, page 173; and Bell, Abstract).

Second, R¹⁰ of claim 19 is selected from (1) phenyl, (2) benzyl, and (3) a 5-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N (wherein (1), (2) and (3) can be optionally substituted). In contrast, the structurally closest

compounds in Kumar, Schane and Bell have , Ac and -CO₂Et (compounds 8, 9 and 10 of Kumar, respectively); -C(O)CH₃ (compound 45,164 of Schane); and -C(O)R or -COOR' (Bell) at the same position.

Therefore it is *not* the case that "[o]ne having ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole" as suggested by the Examiner (Office Action dated Nov. 16 2009, page 4). First, Applicants are unaware of any teaching that would have led a skilled artisan to select the prior art compounds discussed above as lead compounds for further modifications to arrive at claim 19. These compounds were merely disclosed as one of the many compounds rather than superior compounds over the other disclosed compounds. Second, there is no teaching in the cited art that would render trivial a change to the D ring that replaces a H, Ac, -C(O)CH₃, or -C(O)R of the prior art with CF₃ of claim 1 at the Y₂

position. Third, there is no teaching in the cited art to replace , Ac, -CO₂Et, -C(O)CH₃, -C(O)R, or -COOR' of the prior art with phenyl, benzyl or a 5-membered HET of claim 19 at the R¹⁰ position.

Courts have consistently held that a *prima facie* case of obviousness as related to a new chemical compound requires that the prior art provide some suggestion or motivation for making the specific molecular modifications necessary to achieve the claimed invention combined with a reasonable expectation of success. *Takeda v. Alphapharm*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). The court made it clear that "consistent with the legal principles enunciated in *KSR*", there

must be "some reason that would have led a chemist to modify a known compound in a particular manner." *Id* at 1356-1357.

Moreover, the Federal Circuit case *Eisai* affirmed *Takeda* and further elaborated on the 103 obviousness analysis as related to new chemical compounds. *Eisai v. Dr. Reddy's*, 533 F.3d 1353 (Fed. Cir. 2008). The court stated that "[t]o the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable". *Id* at 1359. The court further stated that "post-*KSR*, a *prima facie* case of obviousness for a chemical compound still, in general, begins with reasoned identification of a lead compound. *Teva* cannot create a genuine issue of material fact on obviousness through the unsupported assertion that compounds other than landsoprazole might have served as lead compounds". *Id*. A very recent case *Teva* further affirmed *Takeda* and *Eisai* as to the 103 obviousness standard. *Proctor & Gamble v. Teva*, CAFC 2008-1404, -1405, -1406 (Fed. Cir. 2009).

Here, the chemical art of the instant application is both unpredictable and vast. The Examiner's generalized assertion that "[o]ne having ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole" (Office Action dated Nov. 16 2009, page 4) is simply unsupported by the teachings of the cited art. As discussed above, there are major structural differences between compounds of claim 19 and the compounds disclosed in the cited art. The cited art does not provide any suggestion or motivation to select the right lead compounds and to make the particular molecular modifications necessary to arrive at the instant compounds.

Moreover, in the absence of any teaching or suggestion of the two structural features at the Y₂ and R₁₀ positions of claim 19 by the cited references, there would be no reasonable expectation of success to obtain compounds of claim 19 by modifying the prior art compounds, both from a synthetic point of view as well as because of known differences between Y₂ and R₁₀ of claim 19 and those substituents of the cited art at the corresponding positions.

Thus, claim 19 is not obvious over Kumar, Schane and Bell.

Claims 20 and 21

As an initial matter, claim 20 is merely a re-written independent form of the original claim 20 and includes all limitations of original claims 1, 3 and 20. This amendment is made due to cancellations of original claims 1 and 3 to expedite the prosecution of this application and not for patentability reasons.

In claim 20, Y₂ is hydrogen, X is a bond and R¹⁰ is a 5-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N. Thus, compounds of claim 20 can be distinguished from those disclosed in Kumar, Schane and Bell in at least the following aspect. R¹⁰ of claim 20 is a 5-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N. In contrast, the structurally closest

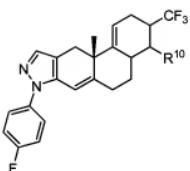
compounds in Kumar, Schane and Bell have , Ac and -CO₂Et (compounds 8, 9 and 10 of Kumar, respectively); -C(O)CH₃ (compound 45,164 of Schane); and -C(O)R and -COOR' at the same position (Kumar, Table 1, page 3281; Schane, Figure 2, page 173; Bell, Abstract).

For similar reasons as presented above under Claim 19 argument, claim 20 is not obvious over Kumar, Schane and Bell as these references fail to provide any reason that would have led a skilled artisan to select the right lead compounds and then modify the lead compounds in the particular manner to arrive at the compounds of claim 20. There would also be no reasonable expectation of success.

Claim 21, which depends from claim 20 and includes additional limitations, is thus also not obvious over the cited art.

Claims 29 and 30

Compounds of claim 29 have the following structure wherein R¹⁰ is a substituted 5-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N (and Y₂ is CF₃):



Id.

Thus, compounds of claim 29 can be distinguished from those disclosed in Kumar, Schane and Bell in at least two aspects. First, Y₂ is CF₃ in claim 29. On the other hand, none of the cited art discloses CF₃ as a substituent at this position. Second, R¹⁰ of claim 29 is a substituted 5-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N. In contrast, none of the cited art discloses a substituted 5-membered aromatic or non-aromatic monocyclic ring as a substituent at this position.

For similar reasons as presented above under Claim 19 argument, claim 29 is not obvious over Kumar, Schane and Bell as these references fail to provide any reason that would have led a skilled artisan to select the right lead compounds and then modify the lead compounds in the particular manner to arrive at the compounds of claim 29. There would also be no reasonable expectation of success.

Claim 30, which depends from claim 29 and includes additional limitations, is thus also not obvious over the cited art.

Claim 22

Claim 22 is an independent claim and includes a list of specific compounds each of which is structurally different from compounds disclosed in the cited art.

Specifically, each compound of claim 22 has at least one structural feature as listed in the following table that is not taught by any of the cited art:

<u>Compound # of Claim 22</u>	<u>Y2 Substituent</u>	<u>R10 Substituent</u>
1-81	CF ₃	N/A
82-86	-COOCH ₃	-COOCH ₃
87-90	N/A	CF ₃ and -COOCH ₃
91	N/A	→ COOCH ₃ (and additional chirality at other positions)
92	N/A	“”“”// COOCH ₃ (and additional chirality at other positions)
93-94	-COOCH ₃	CF ₃ and -COOCH ₃
95-96	N/A	 spiro-connection at *
97	N/A	→ COOCH ₃ (and additional chirality at other positions)
98	N/A	“”“”// COOCH ₃ (and additional chirality at other positions)
99-100	N/A	

101-102

N/A



103

-COOCH₃

CF₃ and -COOCH₃

104-140

CF₃

N/A

For similar reasons as presented above under Claim 19 argument, claim 22 is not obvious over Kumar, Schane and Bell as these references fail to provide any reason that would have led a skilled artisan to select the right lead compounds and then modify the lead compounds in the particular manner to arrive at compounds of claim 22. There would also be no reasonable expectation of success.

In view of the foregoing amendments and remarks, Applicants believe all pending claims are in condition for allowance. Applicants respectfully request withdraw of the §103(a) rejections and allowance of the pending claims.

The Examiner is invited to contact the undersigned attorney at the telephone number provided below if such would advance the prosecution of the instant application. Applicants believe no additional fees are due, but the Commissioner is authorized to charge any fees required in connection with this Response from Merck Deposit Account No. 13-2755.

Respectfully submitted,

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